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Research Article

Kidney Protective Effects of Semaglutide

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Abstract

The glucagon-like peptide 1 receptor (GLP-1R) agonist semaglutide decreases cardiovascular (CV) events in patients with type 2 diabetes or obesity. Post-hoc analyses of these trials suggested several kidney protective actions of semaglutide recorded as secondary outcomes. The FLOW trial is the first dedicated randomized trial designed to examine kidney effects of semaglutide in patients with type 2 diabetes and chronic kidney disease (CKD) and albuminuria. After a median follow-up of 3.4 years, semaglutide (1 mg subcutaneously once weekly) decreased the primary kidney outcome by 24% compared with placebo; hazard ratio (HR) 0.76 (95% CI, 0.66 to 0.88; P=0.0003). Semaglutide slowed kidney function deterioration as reflected by a 1.16 ml/min/1.73 m2 (95% CI, 0.86 to 1.47) slowe decline in annual estimated glomerular filtration rate (eGFR) versus placebo (P<0.001). In addition, there was significant decrease in urinary albumin-to-creatinine ratio (UACR) compared with placebo at week 104. Death from cardiovascular (CV) causes and death from any cause were significantly decreased by semaglutide, HR 0.71 (95% CI, 0.56 to 0.89) and 0.80 (95% CI, 0.67 to 0.95), respectively. A pre-specified analysis of the FLOW trial showed that heart failure was decreased in the semaglutide group, HR 0.73 (95% CI, 0.62 to 0.87; P=0.0005). No significant effects of semaglutide were demonstrated in the small subgroup of patients (15.6%) who were taking sodium-glucose co-transporters 2 (SGLT2) inhibitors at baseline. Rates of serious adverse effects were lower in the semaglutide group (49.6%) than placebo (53.8%). However, eye disorders reported as serious adverse events were more common with semaglutide (3%) than with placebo (1.7%). Proportions of patients who discontinued semaglutide due to adverse effects were 13.2% and 11.9% in the semaglutide group and placebo group, respectively. In conclusion, semaglutide may be a useful addition to slow CKD progression and decrease CV events and mortality in patients with type 2 diabetes and CKD with albuminuria. More frequent eye exam is needed to prevent eye complications of semaglutide.

Keywords: semaglutide; kidney disease; cardiovascular events; flow trial; eye disorders

Introduction

The FLOW is a randomized, double-blind, placebo-controlled, multinational trial [7,8]. It included 3,533 patients with type 2 diabetes and CKD defined as eGFR of 50-75 ml/min/1.73 m^2 and urinary albumin-to-creatinine ratio of >300 and <5,000 mg/g or an eGFR of 25 to < 50 ml/min/1.73 m^2 and a UACR of >100 and < 5,000 mg/g [7,8]. Table 1

Design	Randomized, double-blind, placebo-controlled, multinational, 2 groups: semaglutide n= 1767, placebo n= 1766, median follow-up 3.4 years
Patients' demographics	Age 66.6 years, 30.3% women, 65.8% Whites, 23.9% Asians
Intervention	Semaglutide 1.0 mg qweek (n=1767) vs matching placebo (n=1766)
Baseline glycated hemoglobin	7.8%
Baseline weight, BMI	89.6 kg, 32.0 kg/m2
eGFR, median UACR	47.0 ml/min/1.73 m^2, 567.6 mg/g
Proportions of patients with eGFR < 30 ml/min/1.73 m^2	11.3%
Proportions of patients with UACR	68.5%
Proportions of patients using SGLT2 inhibitors	15.6%

Proportions of patients on RAAS blockade	95.3%
Proportions of patients using insulin	61.4%
Primary outcome	Composite of the following 5 major renal events: onset of kidney failure (dialysis, transplantation, or an eGFR of < 15 ml/min/1.73 m^2), ≥50% reduction in the eGFR from baseline, or death from kidney or CV causes
Secondary outcomes	eGFR slope, major CV events, death from any cause
Reduction in primary outcome by semaglutide	331 vs 410 events with placebo, HR 0.76 (95% CI, 0.66 to 0.88; P=0.0003)
Effect on annual rate of eGFR (ml/min/1.73 m^2)	Semaglutide -2.19 vs placebo -3.36, difference 1.16 (95% CI, 0.86 to 1.47; P<0.001)
Effect on major CV events (CV death, nonfatal MI, nonfatal stroke)	212 events with semaglutide vs 254 events with placebo, HR 0.82 (95% CI, 0.68 to 0.98; P=0.29)
Effect on death from any cause	227 deaths with semaglutide vs 279 deaths with placebo, HR 0.80 (95% CI, 0.67 to 0.95; P=0.01)
Ratio of UACR at week 104 vs baseline	Semaglutide 0.60 vs placebo 0.88; ratio semaglutide/placebo=0.68 (95% CI, 0.62 to 0.75)
Proportions of patients who discontinued treatment due to adverse effects	13.2 % with semaglutide versus 11.9% with placebo
Proportions of patients with eye disorders reported as serious adverse effects	3.0% with semaglutide versus 1.7% with placebo

Abbreviations in table 1: eGFR: estimated glomerular filtration rate, UACR: urinary albumin-to-creatinine ratio, SGLT2: sodium-glucose co-transporters 2, RAAS: renin-angiotensin-aldosterone system blockade, CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio

Summarizes characteristics and main findings of the FLOW trial. Mean age of the FLOW population was 66.6 years, 70% were men, and 65.8% Whites [8]. Approximately 80% of patients had evidence of CKD at baseline as reflected by an eGFR < 60 ml/min/1.73 m^2 with 68% of them considered at very high risk for progression of CKD based on the kidney disease: Improving Global Outcomes risk calculators [9]. Patients were receiving standard care medications with 95% of them already using renin-angiotensin-aldosterone system (RAAS) blockade [8]. The primary outcome of the FLOW trial was a composite of the following 5 major kidney disease events: 1. Persistent ≥50% reduction in the eGFR from baseline, 2. Persistent eGFR of < 15 ml/min/1.73 m^2), 3. Initiation of kidney-replacement therapy, 4. Death from kidney-related causes, 5. Death from CV causes [8]. Patients were randomized into 2 almost equal groups to receive semaglutide 1 mg subcutaneously qweek versus matching placebo. According to a prespecified interim analysis, the trial was terminated early after a median follow-up of 3.4 years, after demonstration of clear benefit in the semaglutide group [8]. Thus, the risk of a primary outcome event was 24% lower in the semaglutide group than in the placebo group; HR 0.76 (95% CI, 0.66 to 0.88; P=0.0003) [8]. Primary outcome in the semaglutide and placebo groups started to diverge after approximately 24 months [8]. Regarding the individual components of the primary outcome, HRs ranged from 0.71 to 0.84 indicating lower event rates in the semaglutide group than the placebo group, except for death from kidney-related causes, 5 deaths in each group [8]. In addition, there was significant decrease in 3 confirmatory secondary outcomes in the semaglutide group versus the placebo group. The first confirmatory outcome was the annual rate of decline in eGFR, -2.19 versus -3.36 ml/min/1.73 m^2 with placebo (estimated difference 1.16; 95% CI 0.86 to 1.47; P<0.001). The second was incidence of major CV events; HR 0.82 (95% CI, 0.68 to 0.98; P=0.029). The third was death from any cause; HR 0.80 (95% CI, 0.67 to 0.95; P=0.01) [8]. The only outcome that occurred numerically in higher number of semaglutide-treated subjects was non-fatal stroke, HR 1.22 (95% CI 0.84 to 1.77) [8].

Subgroup analysis of the FLOW trial

Results were consistent in several patient subgroups classified by gender, age, body mass index (BMI), baseline eGFR, prevalent CV disease and heart failure, glycated hemoglobin, insulin and metformin use [8].

Concomitant use of semaglutide and SGLT2 inhibitors

Clinical trials have demonstrated that SGLT2 inhibitors confer significant benefits in decreasing CV events and slowing CKD in patients with and without diabetes [10]. Hence, SGLT2 inhibitors are recommended as first line therapy in patients with high risk of CV and renal disease [10]. In the FLOW trial, 15.6% of patients were taking SGLT2 inhibitors at baseline. In this small subgroup, no effect of semaglutide on the primary outcome was illustrated; HR 1.07 (95% CI, 0.69 to 1.67; P=0.755), whereas the effect of semaglutide was significant among participants not taking SGLT2 inhibitors at baseline; HR 0.73, 95% CI, 0.63 to 0.85; P<0.001) [8,11]. Yet, the interaction for SGLT2 inhibitors use was not significant (P interaction=0.109) due to the small proportions of patients taking SGLT2 inhibitors. Conversely, in a recent metanalysis of 12 randomized trials, Apperlo et al [12] reported that beneficial effects of SGLT2 inhibitors on progression of CKD were consistent with or without GLP-1 R agonist use, HR 0.65 (95% CI, 0.46 to 0.94) and HR 0.67 (95% CI, 0.62 to 0.72), respectively. These authors also reported similar results with respect to major CV events [12]. In addition, in a cohort study for UK, Simms-Willimas et al [13] reported that the combination of SGLT2 inhibitors and GLP-1 R agonists were associated with lower rates of serious renal and CV events compared to either class alone. Regarding safety of conjunctive use SGLT2 inhibitors and semaglutide, available data suggest that this combination was not associated with any excess or new adverse effects [12]. In view of these conflicting results, efficacy and safety of semaglutide combined with SGLT2 inhibitors have to be further studied in randomized trials comparing kidney endpoints of semaglutide alone versus a SGLT2 inhibitor alone versus both agents.

Concomitant use of GLP-1 agonists and finerenone

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist shown to decrease cardiorenal events in patients with type 2 diabetes in 2 landmark randomized trials: FIDELITY-DKD and FIGARO-DKD [14]. Unfortunately, very few patients in the FLOW trial were taking finerenone [8]. Of 13,026 patients included in the FIDELITY-DKD and FIAGARO-DKD trials, 944 subjects (7.2%) were using a GLP-1 R agonist, mostly liraglutide (64%), dulaglutide (16%), but semaglutide was used by <0.1% of patients at baseline [15]. In a post-hoc analysis of the FIDELITY-DKD and FIGARO-DKD trials, Rossing et al [15] showed that the effect of finerenone on decreasing CV and kidney events were similar irrespective of use of background GLP-1 R agonist [15]. Thus, the combination of semaglutide and finerenone requires further investigations.

Effects of semaglutide on heart failure in FLOW trial

In a pre-specified analysis of the FLOW trial, Prately et al [16] examined effects of semaglutide on a prespecified composite outcome formed of 2 components: heart failure events leading to hospitalization or urgent care visit, or CV death. Over a median follow-up of 3.4 years, the latter composite outcome occurred less frequently in the semaglutide group compared with the placebo group, 3.8 per patient-years (222 events) and 25.1 per patients-year (292 events), respectively; HR 0.73 (95% CI, 0.62 to 0.87; P=0.0005) [16]. Interestingly, these results remained unchanged irrespective of use of baseline use of SGLT2 inhibitors. The latter agents are known to decrease HF events by approximately 30% [12].

Effect of semaglutide on intermediate outcomes

In the FLOW trial, patients randomized to semaglutide lost more weight [4.1 kg (95% CI, 3.65 to 4.56)], had lower glycated hemoglobin levels [0.81 percentage points (95% CI, 0.72 to 0.90)], and lower systolic blood pressure (SBP) [2.23 mmHg (95% CI, 1.13 to 3.33)] compared with placebo [8].

Effects of semaglutide on kidney function in patients without diabetes and largely preserved kidney function

While no study exists to specifically examine semaglutide kidney effects in patients without diabetes, Colhoun et al [6] performed a pre-specified analysis of kidney endpoints in the SELECT trial. The latter trial showed that high-dose semaglutide (2.4 mg subcutaneously once weekly) resulted in 20% reduction in major CV events in obese subjects (mean baseline weight and BMI 96.6 kg and 33.3 kg/m^2, respectively) without diabetes (n=8,803) compared with placebo (n=8,801) after a median follow-up of 182 weeks [6]. The kidney endpoint in the SELECT trial consisted of the following 5 components: death from kidney disease, initiation of kidney replacement therapy (dialysis or transplantation), persistent eGFR <15 ml/min/1.73 m^2, persistent ≥50% reduction in eGFR, or onset of macroalbuminuria [6]. The incidence of the kidney endpoint was lower with semaglutide (1.8%) versus placebo (2.2%); HR 0.78 (95% CI, 0.63 to 0.96; P=0.02) [6]. The benefit in the kidney outcome with semaglutide was mainly driven by reduction in onset of macroalbuminuria and persistent ≥ 50% reduction in eGFR [6]. The amelioration in semaglutide on kidneys was at least in part attributed to the weight-loss caused by semaglutide, -8.5% (95% CI, -8.7 to -8.3) in BMI versus placebo [6].

Effect of semaglutide on primary prevention of diabetic kidney disease

The first large randomized CV trial of semaglutide was the SUSTAIN 6 trial which evaluated the effects of semaglutide 0.5 mg and 1.0 mg once weekly for 104 weeks on CV events in 3,297 patients with type 2 diabetes and high CV risk [2]. In a post-hoc analysis of the SUSTAIN-6 trial, Wang et al [17] examined the effect of semaglutide on new onset diabetic kidney disease (defined as UACR ≥30 mg/g or eGFR <60 ml/min/1.73 m^2) in 1,139 participants who did not have evidence of CKD at baseline. These investigators found that semaglutide significantly decreased the risk of developing diabetic kidney disease versus placebo, OR 0.56, 95% CI, 0.42 to 0.74; P<0.0001 [17]. This benefit was driven by the effects of semaglutide on decreasing incidence of microalbuminuria (UACR of >30 mg/g), whereas it had no effect on decreasing incidence of reaching eGFR < 60 ml/min/1.73 m^2 [17].

Safety of semaglutide in patients with chronic kidney disease

In general, semaglutide 1.0 mg once weekly was fairly tolerated in patients with type 2 diabetes and CKD as reflected by the slightly higher discontinuation rates in the semaglutide group (13.2%) versus placebo (11.9%), mostly due to gastrointestinal disorders (4.5% versus 1.1%) [8]. Interestingly, no increase in severe hypoglycemia was recorded in the semaglutide group versus placebo (47 versus 46 events with placebo). This is a reassuring safety finding given that 61% of participants were using insulin at baseline and the fact that CKD is a strong risk factor for hypoglycemia [18]. However, 2 safety concerns emerged in the FLOW trial. First, eye disorders reported as serious adverse events were more common with semaglutide (3%) than with placebo (1.7%). Diabetic retinopathy complications were also higher with semaglutide in the earlier trial SUSTAIN 6 occurring in 3.0% with semaglutide and 1.8% with placebo, HR 1.76 (95% CI, 1.11 to 2.78; P=0.02) [2]. This adverse effect is somewhat disturbing given the fact that patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from the FLOW trial [7]. Second, as mentioned earlier, non-fatal stroke was numerically increased in the semaglutide group versus placebo (63 versus 51 events), HR 1.22 (95% CI, 0.84 to 1.77) [8]. Meanwhile, in the SUSTAIN 6 trial, frequency of nonfatal stroke was lower with semaglutide versus placebo, 27 and 44 events, respectively, HR 0.61 (95% CI, 0.38 to 0.99; P=0.04) [2]. Thus, whether this finding is true or attributed to chance requires further studies.

Mechanisms of kidney protective effects of semaglutide

The mechanisms underlying the renal benefits of semaglutide are not clear and most likely multifactorial. The reductions in weight, glycated hemoglobin, and SBP may be among the contributing factors, but unlikely to play a major role. A mediation analysis by Mann et al [19] concluded that glycated hemoglobin and SBP mediated renal effects of semaglutide by 26 % and 22%, respectively. Moreover, in their post-hoc analysis of the SUSTAIN 6 trial, Wang et al [17] found that degrees of reduction in incidence of diabetic kidney disease with semaglutide correlated with the magnitude of reductions in glycated hemoglobin, SBP and weight. Direct effects of semaglutide on kidneys cannot be excluded since GLP-1 receptors were demonstrated in various kidney tissues [20]. These effects are being investigated in the ongoing REMODEL trial using magnetic resonant imaging to evaluate semaglutide effects on kidney oxygenation, inflammation and perfusion [7].

limitations of the flow trial

The FLOW trial has several limitations. First, 70% of patients were men, and only 4.5% were Blacks. The latter ethnic group is disproportionally suffering from CKD [21]. Second, being terminated early, after 570 primary events instead of the planned 854 events, treatment effect of semaglutide might be overestimated [22]. Third, only 11% of subjects had baseline eGFR < 30 ml/min/1.73 m^2. Therefore, safety and efficacy of semaglutide in patients with severe kidney disease requires further studies. Fourth, patients with baseline glycated hemoglobin of 10.0% or more were excluded. Fifth, the FLOW trial was not designed to examine the impact of semaglutide in primary prevention of CKD and treatment of CKD in patients without diabetes.

Clinical implications of the Flow trial

Based on the strong data derived from the FLOW trial, semaglutide should be recommended for treatment of patients with type 2 diabetes, CKD and albuminuria on top of RAAS blockade [8]. Since the FLOW trial did not show positive significant effects in patients already using SGLT2 inhibitors, likely due to the small number of participants using SGLT2 inhibitors, it may be premature to routinely add semaglutide to SGLT2 inhibitors until further data become available. Meanwhile, it may be useful to add semaglutide to SGLT2 inhibitors in obese patients with uncontrolled type 2 diabetes and uncontrolled blood pressure because of semaglutide established efficacy in decreasing body weight, glycated hemoglobin, and SBP [8].

Conclusions

Semaglutide is the first GLP-1R agonist shown in a dedicated trial of patients with type 2 diabetes and CKD to slow kidney disease progression. Furthermore, semaglutide decreased rates of CV death and all-cause death by 29% and 20%, respectively. These positive effects were attributed in part to significant reductions in weight, glycated hemoglobin and SBP, but other potential mechanisms are under investigations. Semaglutide was generally well tolerated in patients with CKD and type 2 diabetes. Yet, the increase in frequency of severe eye disorders with semaglutide requires close

monitoring of eye exam. Overall, semaglutide represents a useful addition to the management of patients with type 2 diabetes and CKD.

Conflict of interest

The author has no conflict of interest to declare.

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